

Isoniazid TB preventive therapy

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Enhancing the quality of care

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Overview

- Epidemiology
- Efficacy
- Effectiveness & cost-effectiveness
- Special issues
- TB control

Burden of TB / HIV infection

TB infection

- Globally 1/3 infected
- Asia (46%)
- Africa (31%)
- South Africa (42%)

TB / HIV co-infection

- Africa (2.7%)
- South Africa (8.3% ~ 2 Million people)

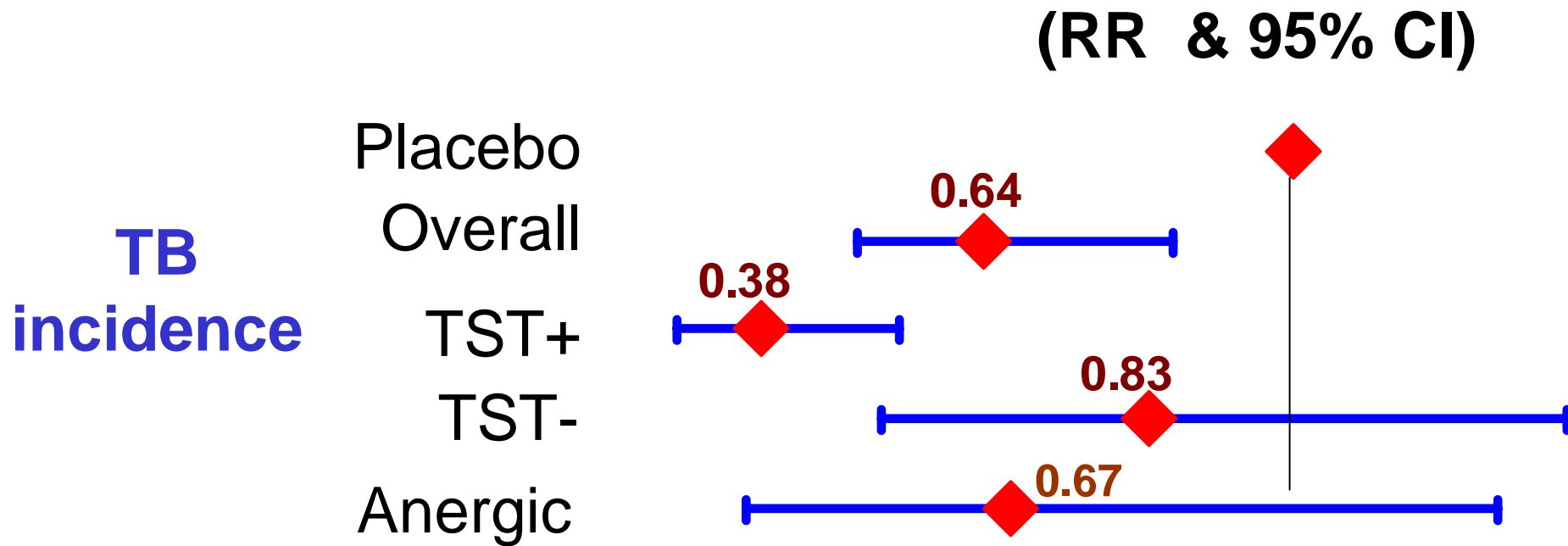
TB risk & duration of HIV infection

	TB	Rate	Unadjusted RR	Adjusted RR
HIV -	289	0.80	1	1
HIV +				
0-1 yr	30	1.6	2.0	2.1 (1.5-3.1)
1-2 yr	29	2.0	2.5	2.3 (1.5-3.3)
2-3 yr	37	3.6	4.5	3.5 (2.4-4.9)
3-4 yr	24	3.5	4.3	2.9 (1.9-4.5)
>4 yrs	18	3.0	4.0	2.6 (1.6-4.2)
P trend			0.001	0.09

Adjusted for age and calendar period

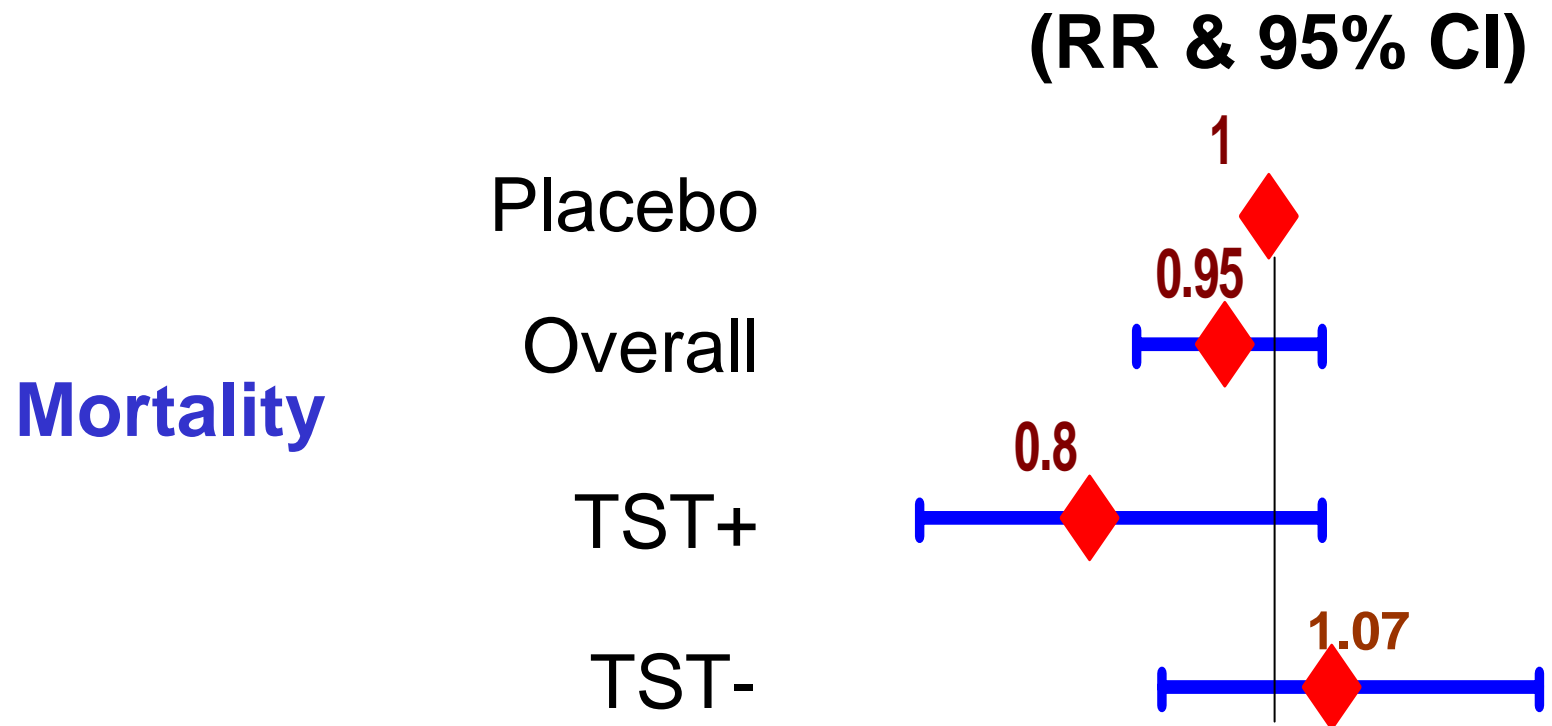
(Sonnenberg P. JID 2005)

Efficacy of primary isoniazid TB preventive therapy



(Woldehanna S. Cochrane infectious disease group. 2004)

Efficacy of primary isoniazid TB preventive therapy



(Woldehanna S. Cochrane infectious disease group. 2004)

Multi-drug TB preventive therapy regimens

- Efficacy compared to INH

TB incidence rate ratio (RR)

- | | |
|----------------------|-----------|
| • INH (13) | RR = 0.67 |
| • INH + RIF (2) | RR = 0.41 |
| • RIF + PZA (4) | RR = 0.54 |
| • INH, RIF + PZA (1) | RR = 0.48 |

- Increased side effects resulting in discontinuation

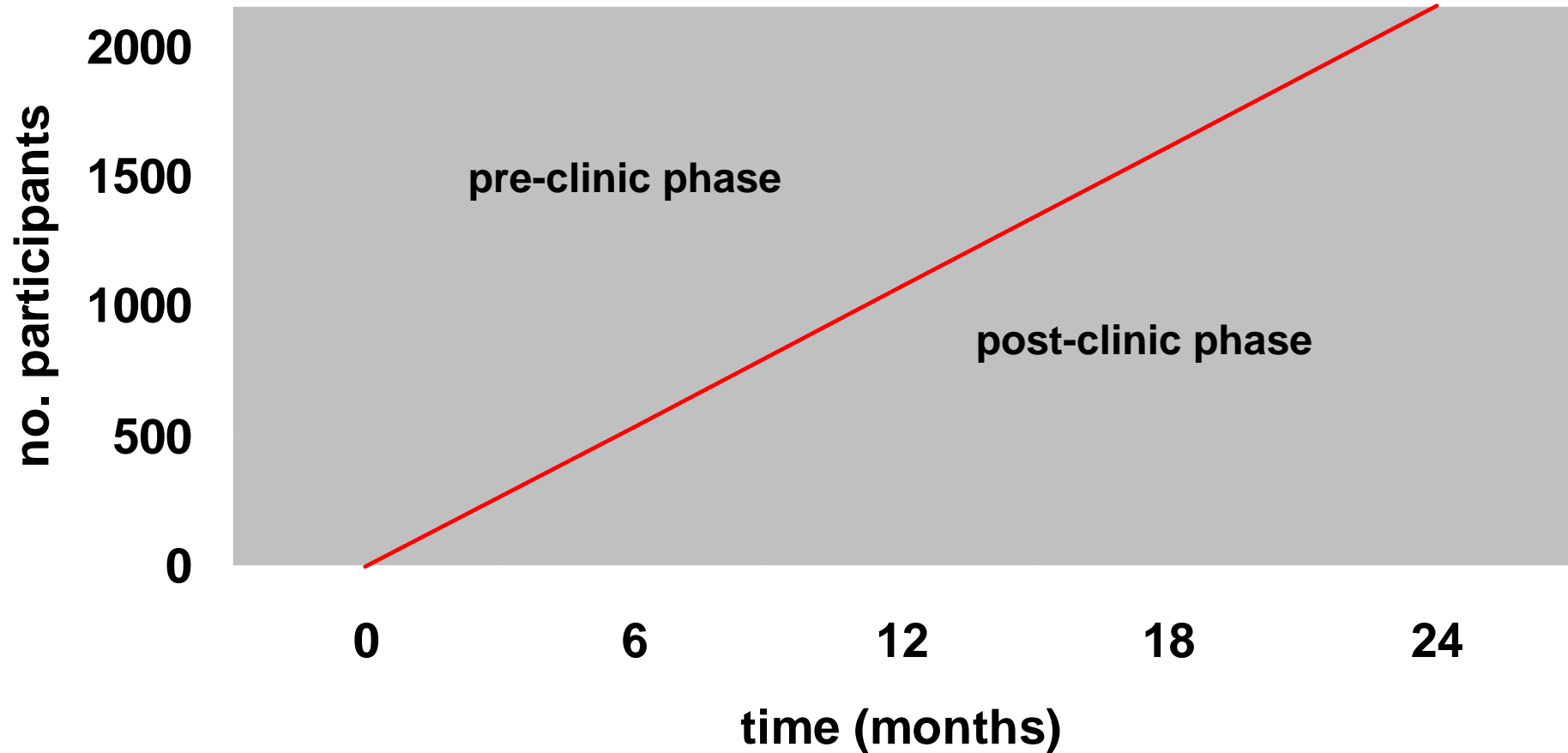
Duration of protection

- Initial protective effect may decline over the short to medium term
- Rifampicin based regimens may have a more durable effect
- Durability may vary with duration of IPT

Adherence

- Ranges from 3% - 69%
- Higher adherence with
 - Modified DOTS
 - Inclusion of TST
 - Shorter regimens

Effectiveness of IPT in a routine clinic



(Grant AD, JAMA, 2005)

TB prevalence at clinic entry

- Overall 5.3%
- CD4 category
 - <200 cells/ μ l 12%
 - >200 cells/ μ l 3.8%

(Day J, Int J Tubercul Lung Dis, In press)

Effectiveness

	IR (per 100 pyrs)		IRR (95%CI)
	Pre-clinic	Post-clinic	
All TB episodes	11.8	9.0	0.68 (0.48-0.96)
Adjusted for time Period	11.9	9.0	0.62 (0.43-0.89)
No previous TB	10.9	8.4	0.54 (0.35-0.83).

(Grant AD, JAMA, 2005)

Cost effectiveness

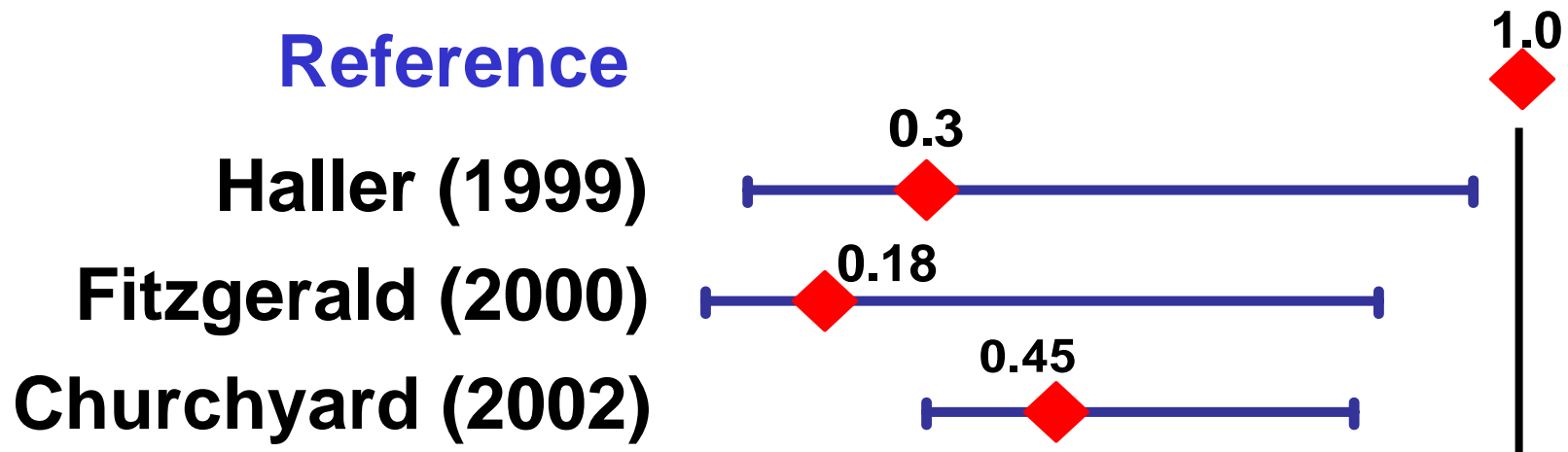
- Costed retrospectively from the providers perspective
- Actual (total) patient costs used
- Costs expressed in 2001 US Dollars
- Cost per TB case averted \$388
- Average cost per TB case treated \$1736

(Kumaranayake L, XV International AIDS Conference, 2004)

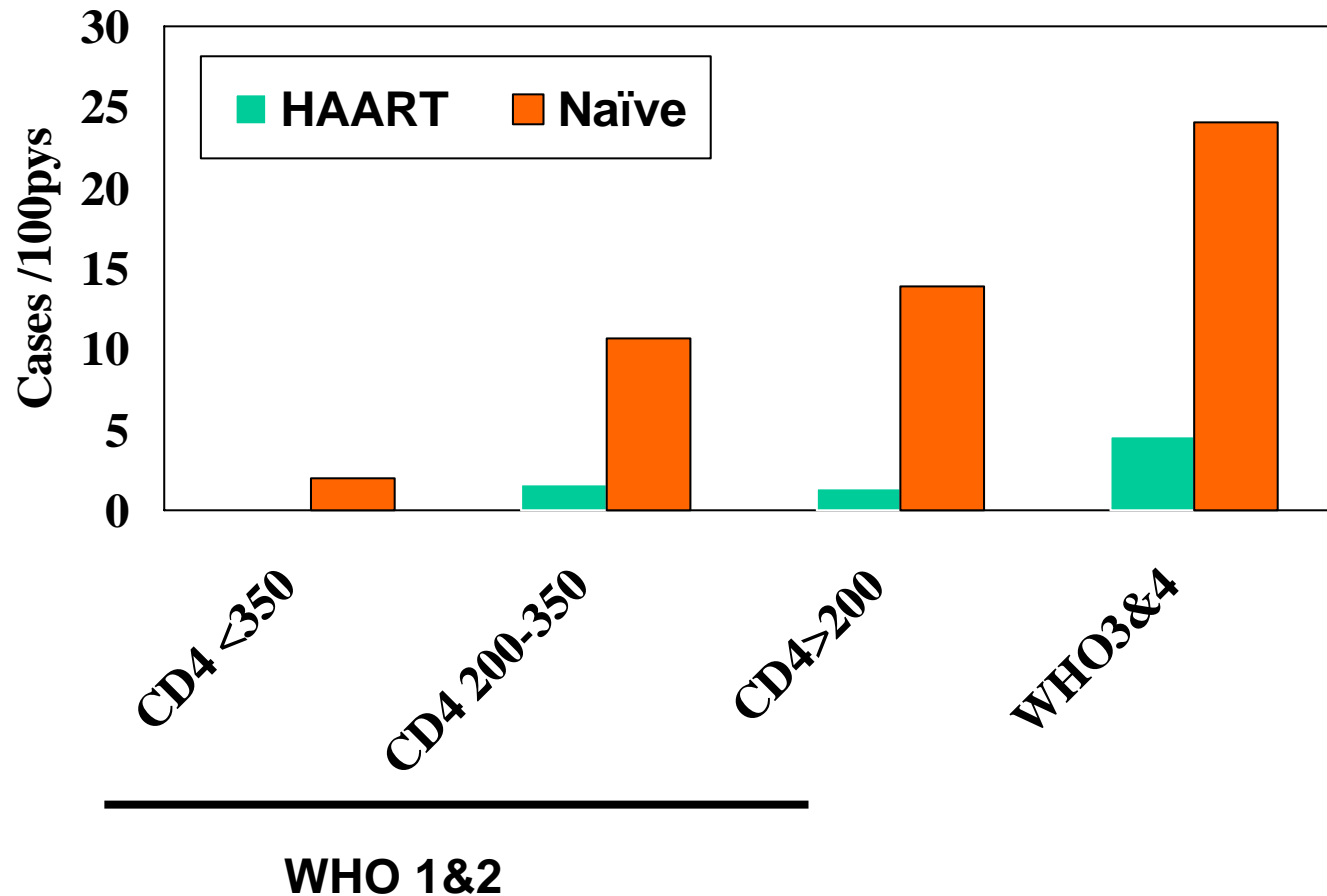
Efficacy of secondary preventive therapy among HIV+ individuals

(Incidence Rate Ratios & 95% CI)

Reference



ART & TB incidence



(Badri, Lancet. 2002)

SPECIAL ARTICLE

Priorities for the Treatment of Latent Tuberculosis Infection in the United States

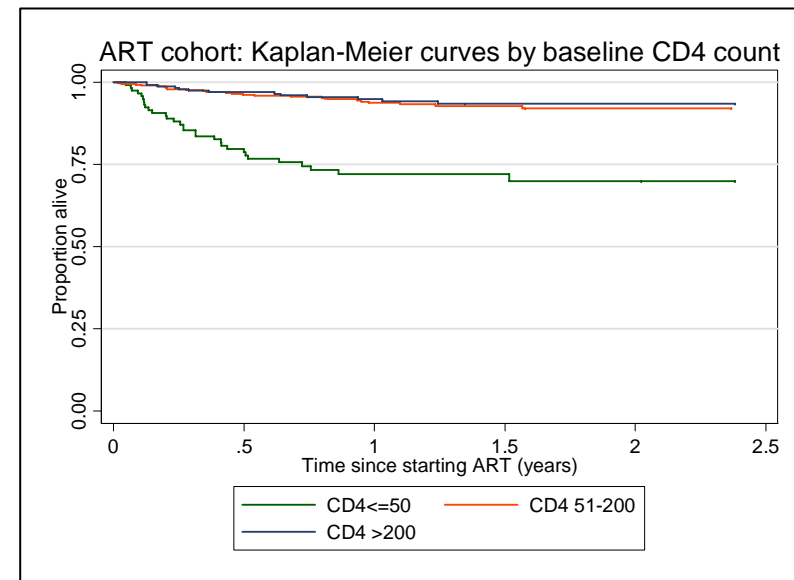
C. Robert Horsburgh, Jr., M.D.

N ENGL J MED 350;20 WWW.NEJM.ORG MAY 13, 2004

However, the risk of tuberculosis among persons receiving effective antiretroviral therapy is still twice that of persons without HIV infection, and the failure of antiretroviral therapy results in reversion to the higher level of risk. Therefore, treatment of latent tuberculosis infection is warranted for all HIV-infected persons with a positive tuberculin skin test.

ART, IPT & Mortality

- Observational cohort study among gold miners
- Individuals starting ART who received INH (previous or current) had 52% reduction in mortality after adjustment for CD4 and previous TB



(Grant AD, HIV Pathogenesis & Treatment. 2005)

Screening for TB prior to PT

- Symptom based questionnaire capable of excluding active TB
- Screening CXR not routinely required to exclude active TB in asymptomatics

(Mosimaneotsile B, Lancet. 2003)

Screening for TB prior to PT

Ongoing CDC sponsored IPT trial in Botswana

- Among asymptomatic HIV-infected Botswanan's screened for TB, 38% had an abnormal chest X-ray

Personal communication: Dr C Wells, CDC

- X-ray changes mostly compatible with TB
- The apparent change in the usefulness of the Chest X-ray thought to be due to progression of the HIV epidemic to a more advanced stage

(Mosimaneotsile B. Int J Tuberc Lung Dis 2005;9:S198)

Effectiveness of TB screening methods

	Sensitivity (%)	Specificity (%)
Symptoms	51.7	75.0
Symptoms/CXR	93.1	49.7

(Day J, Int J Tubercul Lung Dis, In press)

IPT & drug resistance

- Systematic review of published data since 1951
- 13 studies, On IPT = 18095, controls = 17,985
- Summary RR of resistance
 - 1.45 (95% CI 0.85 – 2.47)
- Results similar when stratified by HIV
- findings do not exclude an increased risk of isoniazid-resistant TB after IPT
- Surveillance for isoniazid resistance is required

(Balcells ME, Emerging Infectious Diseases, 2006, In press)

Preventive therapy & drug resistance

- Use of IPT in settings with high background isoniazid resistance uncertain
- Rifampicin monotherapy effective in treating INH resistant TB infection. **Not recommended**

Hepatitis

- Hepatitis is a serious side effect that may result in death if isoniazid is not withdrawn soon after symptoms of hepatitis occurs
- rates of hepatitis: 0.1% - 6.4%
- Death: 0 – 58 per 100,000 persons treated
- Risk factors
 - Age
 - Alcohol use
 - RZ

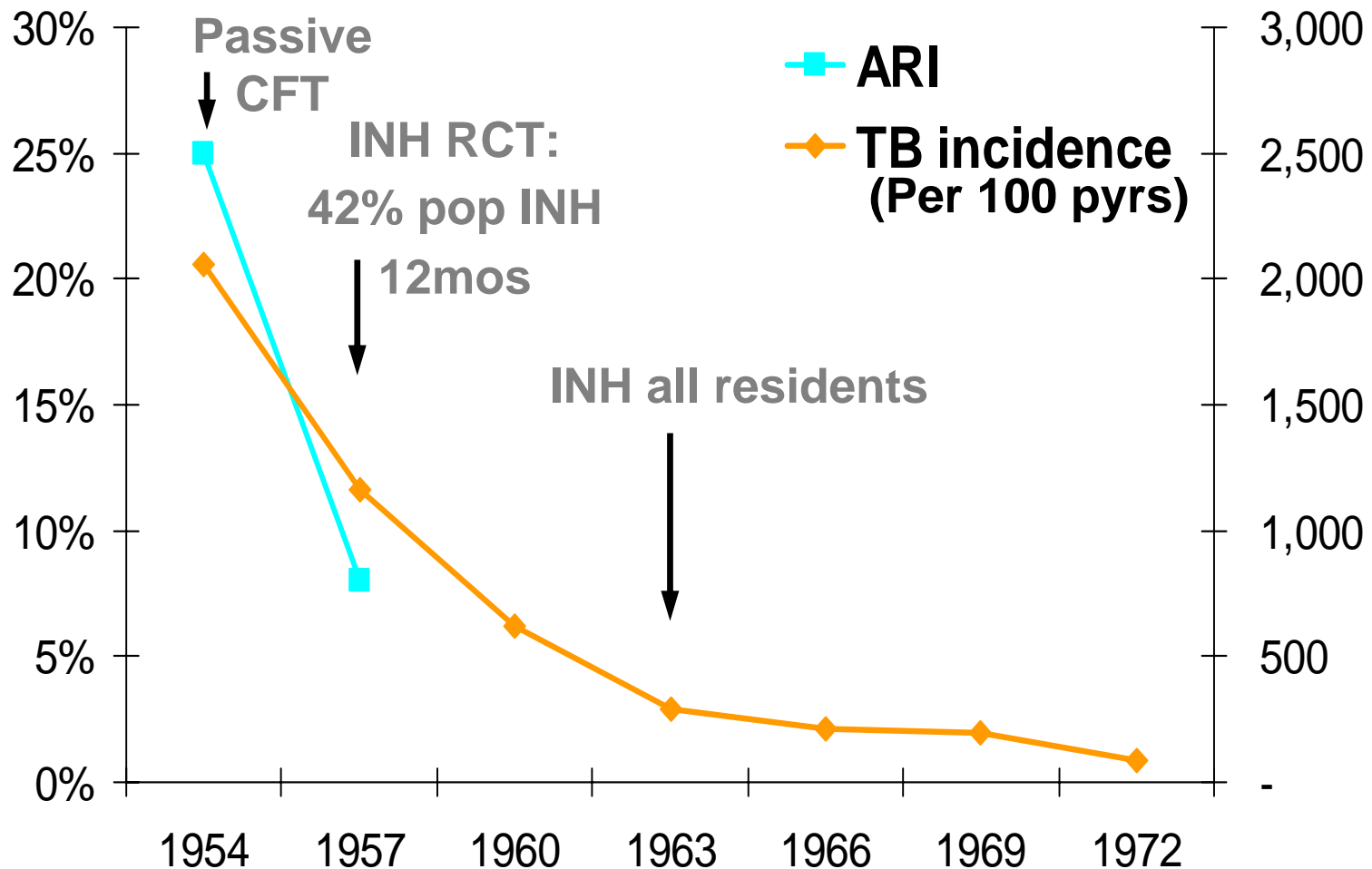
Children

- PT advised for infants and children <5 years exposed to S+ adults
- HIV+ children infected with TB are at high risk of developing TB, particularly severe forms of TB
- TB diagnosis in children is difficult → missed active TB
- TB incidence and mortality halved among HIV-infected children treated with IPT (Zar H, eJIAS, 2004)

Pregnancy

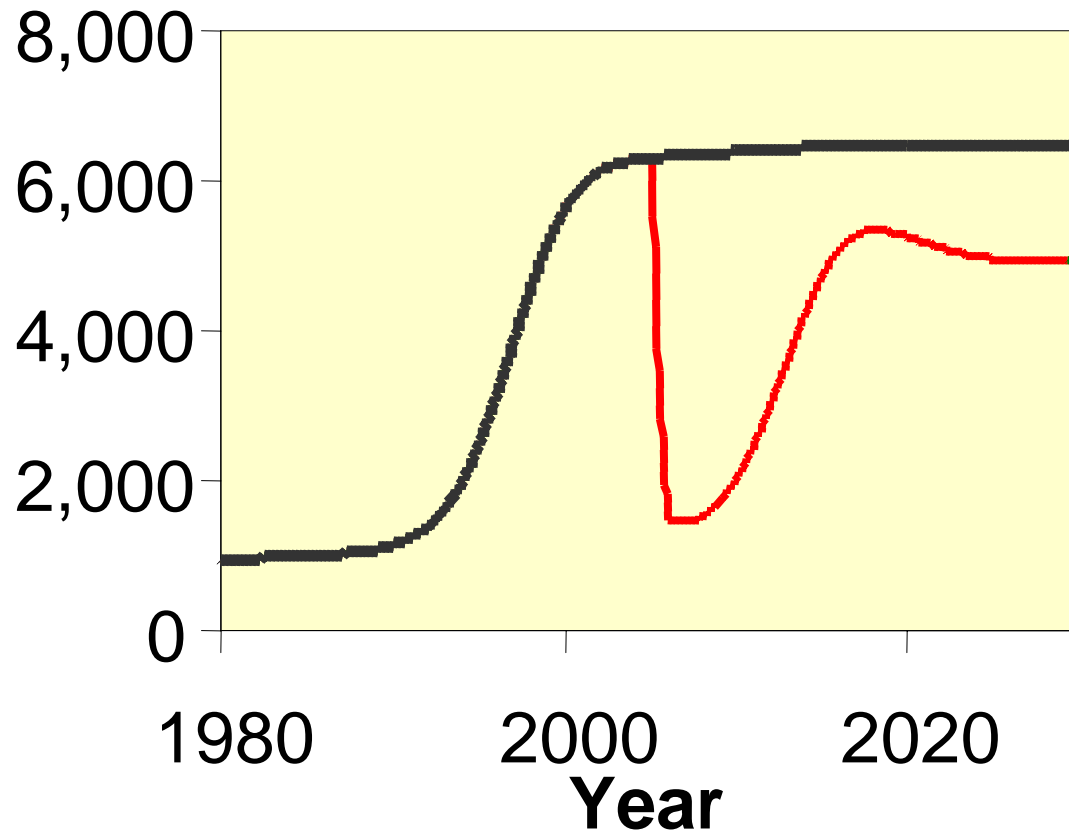
- HIV+ TB causes 10% of maternal deaths in Africa
- Prevalence of active TB in HIV+ pregnant women high
- Spontaneous abortion and obstetric morbidity increased with TB
- Active TB in pregnancy associated with adverse perinatal outcome
- IPT associated with non significant 2.5-fold increase in the risk of hepatitis and 4-fold increase in mortality rate
- PMTCT is a realistic entry point for integrated TB/HIV care and prevention
- Preventing TB in the mother may reduce the risk of TB in infants born to HIV-infected mothers

Community-wide IPT Bethel district, Alaska



Community-wide isoniazid preventive therapy

— Mass PT then Continuous PT
(TB incidence per 100,000 population)



Conclusion

- IPT cost-effective but underutilized
- Safe
- Added benefit of concomitant IPT to ART
- Surveillance for INH resistance required
- IPT may have a role in TB control